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New chemical tools to elucidate the genetics and epigenetics of opioid addiction

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Substance abuse behaviors result from molecular changes to gene expression programs in neurons over time. The addictive nature of morphine and heroin, unlike natural opioid peptides, may result from their cell permeability and thus direct influence on gene expression programs. To probe the broader interactions of the opioids in the cell, we developed chemical tools for visualizing and detecting the opioids in biological systems. We synthesized and evaluated a series of “click-opioids” and “photo-opioids” as probes to track opioid mechanisms in cell culture and mouse model systems of addiction. These probes may be coupled to various reporter strategies for fluorescent imaging, chemical proteomics, or chemical genomics. We employed these probes within a mass spectrometry-based binding site hotspot mapping platform to characterize the direct and indirect interactions of the opioids in the cellular proteome. The strategy involves: (1) treatment of cells with the opioid probe, (2) isolation of the resulting global molecular binding sites, and (3) confident mass spectrometry-based assignment of the opioid conjugated to the protein target. We discovered several novel binding sites to the cellular proteome, including extracellular and intracellular membrane proteins and proteins involved in gene regulation. The global modification site map of the opioid interactome additionally reveals the mode of the interaction with the protein targets by binding, covalent modification, or mediating acetylation marks, and the influence on post-translational modifications that drive gene expression changes. These opioid probes expand the chemical toolbox to study opioid addiction by introduction of a facile mechanism to measure the opioid interactome.